pts engrafted at a md of 22 (11-41) days. 6 pts lost complete chimerism during follow up with proven relapse at a md of 401 days in four. At a md follow up of 23 (4-79) months probability of overall (OS) vs eventfree survival (EFS) was 74% vs 50% for the whole cohort. A trend towards better survival was seen in recipients of related compared to unrelated transplants (100 vs 64 %, p=0.06) and in those with less advanced disease (90 vs 68 % in Dupriez 0 vs 1+2, p=0.26). However the only significant predictor for OS by log rank test was the pretransplant CCI: 85 vs 34 % in pts with CCI 0 to 2 vs 3 to 6 (p=0.01). Probability of EFS at day 480 was significantly less in pts with abnormal karyoptype compared to those with no detectable anomalies (17 vs 61%, p=0.01). Five pts with decreasing chimerism received immunotherapy (3 DLI, 2 PBSC) with return to complete chimerism in three and postDLI aplasia in one.- **Conclusions:** Our results support the use of related and unrelated alloHCT as a curative treatment option in MMM. Outcome is better in pts without disease associated and disease independent comorbidity. For pts with abnormal karyotype there is a considerable risk of relapse/reversal post transplant. Especially in risk pts chimerism therefore should be monitored closely as disease recurrence may respond to immunotherapy.

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UMBILICAL CORD BLOOD TRANSPLANTATION – REPORT OF 106 CASES FROM A SINGLE BRAZILIAN INSTITUTION

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Umbilical cord blood (UCB) has been used as a viable source of hematopoietic stem cell for patients that need transplantation but don't have a suitable related donor. Between 1983 and December 2005, we performed 106 cord blood transplantations (CBT) in our institution. Patients (pts) were treated for malignancies (n=46), Fanconi's Anemia (FA) (n=33) and other nonmalignant disorders (n=27). Median age was 6 (<1-55) years. CB units were related in 14 and unrelated in 92 pts and HLA mismatch was 5/6 in 42 and 4/6 in 38 pts. Transplantation conditioning varied according to the disease. Most pts received Cyclophosphamide with total body irradiation or Bussulfan; 54 pts received antithymocyte globulin (ATG) prior the transplantation. Graft versus host disease (GvHD) prophylaxis consisted of Cyclosporine A (CsA) + methyprednisolone in 68 pts and CsA + Methotrexate in 25 pts. Median nucleated and CD 34 cells were 6.85×10^7/Kg and 1.3×10^5/Kg respectively. Engraftment was reached in 57% of pts. Acute GvHD grade II-IV developed in 46% and extensive chronic GvHD in 18% of pts. The overall survival was 49% after median follow-up of 2.1 years. Engraftment failure (28,3%) was the main cause of death. In the Cox regression analysis ATG in the conditioning regime (p=0.002), HLA compatibility (p=0.03) and infused nucleated cell dose $\geq 3 \times 10$ 7/Kg (p=0.01) were independent predictors of neutrophil engraftment. Age $\leq$ 3 years (p=0.01), bleeding after transplantation (p<0.001) and infection with identified agent (p=0.002) were significantly associated with overall survival. CD 34 cell count and viability, clonogenic capacity, original UCB bank, cryopreservation time, malignant disease status and donor type (related vs unrelated) were not associated with engraftment or overall survival. These results confirm that HLA compatibility and the number of nucleated cells are significantly associated with neutrophil engraftment. We concluded that, despite a high engraftment failure observed, UCB is a feasible source for transplantation.

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DEMONSTRATION OF A SINGLE MIHA SPECIFICITY RECOGNIZED BY MEMORY CD8 T CELLS WHICH INDUCES RESISTANCE TO MHC-MATCHED HEMATOPOIETIC ALLOGRAFTS

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T cells that recognize transplantation antigens arise in sensitized individuals following multiple blood transfusions or marrow transplants as well as in multiparous females. Resistance to allogeneic hematopoietic cell transplantation (HCT) in such sensitized individuals is consistent with the presence of a host memory T cell (TM) population specific for donor cell antigens. We hypothesized that a single donor minor histocompatibility (MiHA) epitope could elicit antigen-specific CD8 TM capable of resisting MHC-matched allogeneic hematopoietic cell engraftment. To address this question, B6 mice were sensitized 2X to the H60 immunodominant MiHA epitope utilizing marrow-derived dendritic cells pulsed with the H60 (LTFNYRNL) peptide. Three weeks following booster sensitization, circulating CD8 TM ($CD44^{hi}$, Ly $6C^+$) were detected by tetramer staining. B6 ($H2^b$) mice containing $CD8^+$ $H60^+$ T cells were subsequently conditioned with 9.0 Gy TBI and transplanted with 5×10^6 BALB.B ($H2^b$) BM-TCD. One week post-transplant, naive recipients of BALB.B ($H60^+$) or B6-H60 congenic TCD-BM contained >10-fold higher levels of circulating donor cells than the B6 dendritic cell/peptide sensitized recipients. Donor progenitor cells were also significantly reduced in sensitized recipients of allogeneic TCD-BM at this time. In contrast, two weeks post-HCT, recipients of syngeneic marrow exhibited >10-fold greater frequency of circulating donor cells compared to recipients of MHC-matched allogeneic marrow (< 5% donor chimerism was detected). These findings demonstrate that host T cells against a single donor MiHA determinant are sufficient to induce resistance to MHC-matched allogeneic marrow engraftment. These effector responses during HVG stand in contrast to those by donor T cell responses post-HCT in which single MiHA differences fail to induce GVHD. Finally, heterologous immunity to virus generates allo-reactive TM cells. Since such TM repertoires could include specificity for MiHA immunodominant epitopes, the presence of TM populations that can mediate resistance in 'naïve' recipients may be more prevalent than previously considered.

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SAFETY AND EFFICACY OF HIGH-DOSE BUSULFAN BY 90-HOUR CONTINUOUS INFUSION IN HEMATOLOGIC MALIGNANCY PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTS

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Busulfan is used in allotransplantation for patients with hematologic malignancies. IV busulfan has recently become available and is widely used qd or qid x 4 with fludarabine in both ablative and reduced-intensity regimens. We have previously demonstrated the benefit of using a test-dose of IV busulfan to predict the systemic exposure of this drug (Walko, ASCO, 2005) and report here on this approach in pts receiving a 90 hr continuous infusion of full-dose busulfan. **Methods:** All pts received a 0.8 mg/kg test dose administered over 2 hours and PK sampling at times 0, 2.5, 4, 5, and 6 hours. Pts began treatment with 30 mg/m2 fludarabine qd x 5 and either 0.8 mg/kg ABW IV busulfan (18 pts) or targeted busulfan to achieve an AUC of 4800 (6 pts) or 5700 (5 pts) umole/min/hr/day on days –7 to –3. PK sampling was done at hours 0, 12, 16, 18, 48, 60, 72, and 89.5. All pts received tacrolimus and 0 (9 pts), 1 (10 pts), 2 (8 pts) or 3 (2 pts) doses of 30 mg of IV alemtuzamab based on disease and donor type for prevention of GVHD prior to initiation of chemotherapy. The initial 18 pts were studied without dose adjustments, followed by dose escalation with targeted systemic exposure of the busulfan and dose adjustments as needed in the last 11 pts treated. **Results:** 29 pts (15 MRD, 14 MUD) ages 18-55 (median 40) with high-risk AML (15), ALL (5), CML (2), IMF (2), MDS (2), or other diseases (3) were enrolled. All pts engrafted with a median of 14 days to an ANC > 500 and 7 days to a platelet count > 20K. No regimen-related deaths were observed in the first 100 days post-transplant. Two patients had transient grade 3 hepatitis and two had grade 3 mucositis. There have been no cases of VOD, pulmonary fibrosis, alveolar hemorrhage or CNS toxicity. One death at day 190 from pneumonia and one at day 191 from hemorrhagic cystitis and enterococcal sepsis occurred for a non-relapse mortality rate of 7%. 14 pts have developed grade 2, one grade 3 and one grade 4 aGVHD. 6 have extensive and 2 have limited

cGVHD. 12 pts have relapsed at a median of 128 days (range 76-512) post transplant with a one year actuarial OS of 65%. **Conclusion:** This approach permits accurate delivery of a targeted systemic exposure to IV busulfan, is well-tolerated, and will allow additional dose escalation. Relapse, as opposed to toxicity, remains the major challenge.

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TREOSULFAN: AN ATTRACTIVE ALTERNATIVE IN THE CONDITIONING IN BONE MARROW TRANSPLANT FOR THALASSEMIA

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Traditionally Busulfan and Cyclofosfamide are used with or without serotherapy in the conditioning for beta thalassemia. Due to a high rejection rate in our institution, Melfalan has been added resulting in a marked reduction of rejection. Toxicity of this regimen is tolerable and consists mainly of mucositis and occasionally of VOD.

Treosulfan is an alkylating agent with a supposedly lower toxicity profile than other alkylating agents.

In 12 previously treated thalassemia patients (class 2-3) conditioned with Busulfan, Melfalan, Cyclofosfamide and serotherapy, mucositis WHO grade 1-2 was seen in 2 patients and grade 3– 4 in 9 patients. VOD was seen in 4 patients and 2 patients had mild VOD. One patient died due to MOF. Acute GVHD was seen in 6 patients. Chronic GVHD (mild) in 2 patients. Two patients rejected but were successfully retransplanted. Ten patients had full donor chimerism, two patients showed stable mixed chimerism.

In comparison the results in 5 beta thalassemia patients (class 2-3) conditioned with Treosulfan 10 -14 mg/m2, Cyclofosfamide 120 mg/kg, Melfalan 140 mg/m2 with additional serotherapy (either ATG or Campath). Two patients had a matched unrelated donor, 3 patients had identical related donors. Three patients received Treosulfan 10 mg/m2. One patient rejected early and was successfully retransplanted with Treosulfan 14 mg/m2. The remaining two patients received Treosulfan 14 mg/m2. Engraftment was in normal range. No acute or chronic GVHD was seen. Mucositis was limited in 3 (WHO grade 2) and moderate to severe (WHO grade 3-4) in 2 patients. No VOD was seen. Chimerism was stable mixed in 2 and full donor in three.**Conclusion:** Treosulfan 14 mg/m2 is well tolerated in thalassemia bone marrow transplant patients and shows a lower toxicity profile than busulfan.

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IMPACTS OF COMORBIDITIES ON OUTCOMES OF PATIENTS (PTS) YOUNGER THAN 60 YEARS OLD, DIAGNOSED WITH INDOLENT MALIGNANCIES AND TREATED WITH ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT): A MODEL FOR PTS WITH AUTOIMMUNE DISEASES

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The NIH has stated the growing need to explore the therapeutic and curative potential of allogeneic HCT for autoimmune diseases (BBMT 2005, 11:862). The safety of HCT in pts with significant comorbidities is of a concern. Here, we analyzed whether the HCT-CI, a sensitive tool to capture comorbidities (Blood 2005, 106:2912), could assess how young (<60 year old) pts with indolent malignancies tolerated allogeneic HCT strategies as a hypothetical model for pts with autoimmune diseases. A majority of pts received myeloablative (MA) conditioning (n=364) with cyclophosphamide plus busulfan (79%) or 12 Gy TBI (21%), while a small group of pts (n=79) received nonmyeloablative (NMA)-conditioning with 2 Gy total body irradiation (18%) ± 90 mg/m^2 of fludarabine (82%). Diagnoses were acute myeloid leukemia in 1st remission (27%), chronic myeloid leukemia-chronic phase (40%), myelodysplasia-refractory anemia (16%), chronic lymphocytic leukemia (8%), low grade non-Hodgkin lymphoma (4%), and others (5%). At HCT, NMA-pts differed from MA-pts with respect to age (median 52 vs 41 years,), prior high-dose HCT (9% vs 1%), unrelated grafts (42% vs 31%), and G-PBMC as stem cell source (87% vs 49%). HCT-CI scores of 1-2 and ≥3 were found among 33% and 35% of NMA vs 35% and 17% of MA-pts, respectively. The most frequent comorbidities were pulmonary (24%) and hepatic (16%). After HCT, 4-year cumulative incidences of non-relapse mortality (NRM) were 10%, 17%, and 36% for MA-pts with HCT-CI scores of 0, 1-2, and ≥3, respectively. Proportional hazards models; adjusted for stem cell source, pt age, donor type, and diagnoses, were used to estimate hazard ratios (HR) for NRM and survival. MA-pts with HCT-CI scores of 1-2 or ≥3 had higher adjusted HRs for NRM (1.85, p=0.06 and 4.56, p<0.0001) and all-cause mortality (2.15, p=0.003 and 4.59, p<0.0001) compared to pts with HCT-CI scores of 0. There were no statistically significant differences in NRM between NMA and MA-pts with HCT-CI scores of 0, 1-2, or ≥3 (p=0.7, p=0.1, p=0.18, respectively); however, the small numbers of pts receiving NMA conditioning in each stratum limited the power of these comparisons. We conclude that among young pts with indolent malignancies, NRM and survival are strongly associated with comorbidity after MA-HCT. Therefore, MA-HCT for treatment of autoimmune diseases might be contraindicated for pts with HCT-CI scores of ≥3. Additional data are needed to clarify the usefulness of NMA-HCT in indolent diseases.

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OUTCOME OF PATIENTS ACCORDING TO ETHNIC GROUPS RECEIVING ALLOGENEIC STEM CELL TRANSPLANTATION IN MALAYSIA

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A total of 106 patients received an allogeneic stem cell transplantation at Kuala Lumpur Hospital between 5/1999 and 5/2006. Majority received G-CSF stimulated bone marrow as stem cell source while 20% received PBSC. The race distribution were 52% Malays, 31% Chinese, 9% Indians and 9% other races. The median time to neutrophil engraftment was 19 days and platelet engraftment was 18 days. There was no difference in engraftment days of platelets and neutrophils between G-CSF stimulated marrow and PBSC. The overall survival OS was 61%, event-free survival EFS was 54% and the 100-day transplant mortality rate TRM was 16%. The cumulative relapse rate was 24% and the graft-vs-host disease GVHD rate was 32%.

The overall survival rate according to race was 62% in Malays, 68% in Chinese and 50% in Indians. The cause for mortality in the Malay race was GVHD at 52%, relapse 29% and infection 29%. Amongst the Chinese, the major cause for mortality was relapse 60%, GVHD 20% and infection 10%. In the other races, the cause of mortality was relapse in 70% and GVHD in 20%.

The incidence of moderate Grade II and severe Grade III-IV acute GVHD was 40% and 29% in the Malays, 43% and 10% in the Chinese and 22% and 22% in the Indians respectively. Similarly the incidence of limited and extensive chronic GVHD was 12% and 34% in the Malays, 21% and 18% in the Chinese and 0% and 38% in the Indians.

It is evident that the incidence of severe acute GVHD and extensive chronic GVHD is higher in the Malays than the other races. Severe GVHD was also the major cause of mortality amongst the Malays than the other races. However the rate of relapse was inversely lower in the Malays than in the Chinese and Indians.

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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN IMATINIB ERA: A SINGLE CENTER COMPARATIVE ANALYSIS OF IMATINIB RECEIVING PATIENTS TO IMATINIB NAIVE PATIENTS

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